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The application was originally filed in English.

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NEW COMPOUNDS

Field of the Invention

The present invention relates to new compounds of formula I, as a free base or salts thereof, to pharmaceutical compositions containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of compounds of formula I and to new intermediates used in the preparation thereof.

Background of the Invention

The neurokinins, also known as the tachykinins, comprise a class of peptide neurotransmitters which are found in the peripheral and central nervous systems. The three principal tachykinins are Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB). At least three receptor types are known for the three principal tachykinins. Based upon their relative selectivities favouring the agonists SP, NKA and NKB, the receptors are classified as neurokinin 1 (NK_1), neurokinin 2 (NK_2) and neurokinin 3 (NK_3) receptors, respectively.

There is a need for an orally active and blood brain barrier crossing dual NK_1/NK_2 receptor antagonist for the treatment of e.g. respiratory, cardiovascular, neuro, pain, oncology, inflammatory and/or gastrointestinal disorders. In order to increase the therapeutic index of such therapy it is desirable to obtain such a compound possessing no or minimal toxicity as well as being selective to said NK receptors. Furthermore, it is considered necessary that said medicament has favourable pharmacokinetic and metabolic properties thus providing an improved therapeutic and safety profile such as lower liver enzyme inhibiting properties.

It is well known that severe problems such as toxicity may occur if plasma levels of one medication are altered by the co-administration of another drug. This phenomenon - which is named drug-drug interactions – could happen if there is a change in the metabolism of one drug caused by the co-administration of another substance possessing liver enzyme

inhibiting properties. CYP (cytochrome P450) 3A4 is the most important enzyme in the human liver as a majority of oxidised drugs have been biotransformed by this enzyme. Accordingly, it is undesirable to employ a medication having a significant degree of such liver enzyme inhibiting properties. It has now been found that many NK receptor antagonists known in the art inhibit the CYP3A4 enzyme to a certain level and consequently there is a possible risk if high doses of those compounds are being used in therapy. Thus, there is a need for a novel dual NK_1/NK_2 receptor antagonist with improved pharmacokinetic properties. The present invention provides compounds with CYP3A4 enzyme inhibiting properties at a low level, as comparatively high IC_{50} values are obtained in a CYP3A4 inhibiting assay. Said method for determining CYP3A4 inhibition is described in Bapiro et al; Drug Metab. Dispos. 29, 30-35 (2001).

Prior Art

EP 0625509, EP 0630887, WO 95/05377, WO 95/12577, WO 95/15961, WO 96/24582, WO 00/02859, WO 00/20003, WO 00/20389, WO 00/25766, WO 00/34243, WO 02/51807 and WO 03/037889 disclose piperidinylbutylamide derivatives, which are tachykinin antagonists.

"4-Amino-2-(aryl)-butylbenzamides and Their Conformationally Constrained Analogues. Potent Antagonists of the Human Neurokinin-2 (NK_2) Receptor", Roderick MacKenzie,A., et al, Bioorganic & Medicinal Chemistry Letters, In Press, available online 15 May 2003, discloses the compound *N*-[2-(3,4-dichlorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]-*N*-methylbenzamide which was found to possess functional NK_2 receptor antagonistic properties.

WO 96/05193, WO 97/27185 and EP 0962457 disclose azetidinylalkyllactam derivatives with tachykinin antagonist activity.

EP 0790248 discloses azetidinylalkylazapiperidones and azetidinylalkyloxapiperidones, which are stated to be tachykinin antagonists.

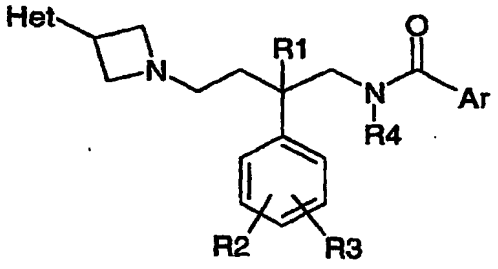
WO 99/01451 and WO 97/25322 disclose azetidinylalkylpiperidine derivatives claimed to be tachykinin antagonists.

EP 0791592 discloses azetidinylalkylglutarimides with tachykinin antagonistic properties.

Disclosure of the Invention

An object of the present invention is to provide tachykinin antagonists having blood brain barrier penetrating properties, improved pharmacokinetic and metabolic properties and/or improved selectivity for the NK_1/NK_2 receptors.

Accordingly, the present invention provides a compound having the general formula (I)



(I)

wherein

Het is a heterocyclic ring containing one or more nitrogen atoms

R1 is hydrogen, hydroxy or lower alkyl

R2 and R3 are independently hydrogen, lower alkoxy, halo, CF_3 or cyano, provided that both are not hydrogen

R4 is lower alkyl

Ar is an optionally substituted aromatic ring system selected from phenyl, pyridinyl, 1-naphthyl, 5,6,7,8-tetrahydro-1-naphthyl, quinolinyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinazolin-4-yl, 1-benzo[b]thiophen-7-yl, 1-benzo[b]thiophen-4-yl, 1-benzo[b]thiophen-3-yl, isoquinolinyl, quinazolinyl and indan-4-yl,

as a free base or any salt thereof

with the proviso that compounds of formula (I) wherein Ar is unsubstituted phenyl are excluded.

Het is a heterocyclic ring containing one or more nitrogen atoms. The heterocyclic ring is preferably connected to the rest of the molecule at one of the nitrogen atoms of the ring. Examples of such heterocyclic rings are optionally substituted piperidino, optionally substituted azepano, optionally substituted pyrrolidino, optionally substituted morpholino, optionally substituted oxazepano, optionally substituted thiomorpholino, optionally substituted thiazepano and optionally substituted piperazino; preferably piperidino optionally substituted at its four position with hydroxy, oxo, methylthio, methylsulfinyl, methylsulfonyl, cyano, 1,3-dioxolan-2-yl, lower alkoxy, amino optionally mono or disubstituted with lower alkyl, acylamino optionally N-substituted with lower alkyl, (lower alkylsulfonyl)amino optionally N-substituted with lower alkyl, or one or two fluoro atoms, pyrrolidino optionally being substituted at its three position with fluoro, hydroxy or oxo, morpholino, thiomorpholino optionally being substituted at its sulfur with one or two oxygen or piperazino optionally being substituted at the 4-nitrogen atom with lower alkyl, lower alkyl sulfonyl, lower acyl or lower alkyl together with oxygen.

R1 is hydrogen, hydroxy or lower alkyl. Preferably, R1 is hydrogen.

R2 and R3 are independently hydrogen, lower alkoxy, halo, CF_3 or cyano, provided that both are not hydrogen. Favourably, R2 and R3 are both chloro or one is fluoro and the other is hydrogen. In a preferred aspect R2 and R3 are both chloro and attached in the three

and four position of the phenyl ring or R2 is fluoro attached in the four position and R3 is hydrogen.

R4 is lower alkyl. Preferably, R4 is methyl.

Ar is an aromatic ring system selected from substituted phenyl, pyridinyl, 1-naphthyl, 5,6,7,8-tetrahydro-1-naphthyl, quinolinyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinazolin-4-yl, 1-benzo[b]thiophen-7-yl, 1-benzo[b]thiophen-4-yl, 1-benzo[b]thiophen-3-yl, isoquinolinyl, quinazolinyl and indan-4-yl. Ar may optionally be substituted at one or more of its carbon atoms in its aromatic moiety with one or more groups independently selected from cyano, halo, lower alkyl, lower alkoxy, nitro, trifluoromethoxy, difluoromethoxy, trifluoromethyl, lower alkylsulfinyl, lower alkylsulfonyl, lower alkylthio and trifluoromethylsulfonyloxy.

One aspect of the invention relates to compounds of formula I, wherein
Het is thiomorpholino, morpholino or oxidothiomorpholino,
R1 is H,
R2 and R3 are fluoro and hydrogen, respectively, fluoro being preferably in para position,
Ar is 3-cyano-5,6,7,8-tetrahydro-1-naphthyl.

In a further aspect of the invention the following compounds are provided:

N-[(2S)-2-(3,4-Dichlorophenyl)-4-(3-oxidothiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-3,5-bis(trifluoromethyl)benzamide acetate,

3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide acetate,

3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide acetate,

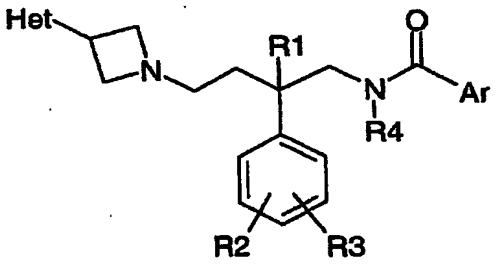
3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(4-hydroxypiperidin-1-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide,

3-cyano-*N*-[2-(4-fluorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide,

3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(4-hydroxypiperidin-1-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide, and

4-fluoro-*N*-[2-(4-fluorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide.

Still another aspect of the invention is a compound having the general formula (I)



(I)

wherein

Het is a heterocyclic ring containing one or more nitrogen atoms

R1 is hydrogen, hydroxy or lower alkyl

R2 and R3 are independently hydrogen, lower alkoxy, halo, CF_3 or cyano, provided that both are not hydrogen

R4 is lower alkyl

Ar is an optionally substituted aromatic ring system selected from substituted phenyl, pyridinyl, 1-naphthyl, 5,6,7,8-tetrahydro-1-naphthyl, quinolinyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinazolin-4-yl, 1-benzo[b]thiophen-7-yl, 1-benzo[b]thiophen-4-yl, 1-benzo[b]thiophen-3-yl, isoquinolinyl, quinazolinyl and indan-4-yl

as a free base or any salt thereof.

The present invention relates to the use of compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

The compounds of the present invention are capable of forming salts with various inorganic and organic acids and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, cyclohexyl sulfamate, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, nitrate, oxalate, palmoate, persulfate, phenylacetate, phosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), and undecanoate. Non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

Pharmaceutically acceptable salts may be prepared from the corresponding acid in conventional manner. Non-pharmaceutically-acceptable salts may be useful as intermediates and as such are another aspect of the present invention.

Acid addition salts may also be in the form of polymeric salts such as polymeric sulfonates.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

The compounds of formula I have one or more chiral centres, and it is to be understood that the invention encompasses all optical isomers and diastereomers that possess dual NK_1/NK_2 antagonistic activity.

It is to be understood that the present invention also relates to any and all tautomeric forms of the compounds of formula I.

Some compounds can exist as a mixture of conformational isomers. The compounds of this invention comprise both mixtures of, and individual, conformational isomers.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions of that group.

In this specification, unless stated otherwise, the term "lower alkyl" includes both straight and branched chain C_{1-4} alkyl groups. Lower alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl.

The term "lower alkoxy" as used herein, unless stated otherwise includes "lower alkyl"O groups in which "lower alkyl" is as hereinbefore defined. Lower alkoxy may be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy or t-butoxy.

The term "lower alkylthio" as used herein, unless stated otherwise includes "lower alkyl"S groups in which "lower alkyl" is as hereinbefore defined. Lower alkylthio may be methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-butylthio or t-butylthio.

In this specification, unless stated otherwise, the term "halo" includes chloro, bromo, fluoro and iodo.

In this specification, unless stated otherwise, the term " lower alkyl sulfonyl " includes lower alkyl sulfonyl groups in which "lower alkyl" is as hereinbefore defined. Lower alkyl sulfonyl may be methylsulfonyl, , ethylsulfonyl, n-propylsulfonyl, i-propylsulfonyl, n-butylsulfonyl, i-butylsulfonyl, s-butylsulfonyl or t-butylsulfonyl.

In this specification, unless stated otherwise, the term "lower alkylsulfinyl " includes lower alkyl sulfinyl groups in which "lower alkyl" is as hereinbefore defined. Lower alkyl sulfinyl may be methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, i-propylsulfinyl, n-butylsulfinyl, i-butylsulfinyl, s-butylsulfinyl or t-butylsulfinyl.

In this specification, unless stated otherwise, the term "lower acyl" includes formyl, acetyl, propionyl, butyryl and isobutyryl.

Pharmaceutical Formulations

According to one aspect of the present invention there is provided a pharmaceutical formulation comprising a compound of formula **I**, as a single enantiomer, a racemate or a mixture thereof as a free base or pharmaceutically acceptable salts thereof, for use in

prevention and/or treatment of respiratory, cardiovascular, neuro, pain, oncology, imflammatory and/or gastrointestinal disorders.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation or insufflation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, pellets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to herein.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.01 to 25 mg/kg body weight (and preferably of 0.1 to 5 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention. For example a tablet or capsule for oral administration may conveniently contain up to 250 mg (and typically 5 to 100 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof. In another example, for administration by inhalation, a compound of the formula (I) or a pharmaceutically acceptable salt thereof may be administered in a daily dosage range of 5 to 100 mg, in a single dose or divided into two to four daily doses. In a further example, for administration by intravenous or

intramuscular injection or infusion, a sterile solution or suspension containing up to 10% w/w (and typically 5% w/w) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof may be used.

Medical and Pharmaceutical Use

The present invention provides a method of treating or preventing a disease condition wherein antagonism of tachykinins acting at the NK_1 and NK_2 receptors is beneficial which comprises administering to a warm-blooded animal an effective amount of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof. The present invention also provides the use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in a disease condition wherein antagonism of tachykinins acting at the NK_1 and NK_2 receptors is beneficial.

The compounds of formula (I) or pharmaceutically acceptable salts or solvates thereof may be used in the manufacture of a medicament for use in the prevention or treatment of respiratory, cardiovascular, neuro, pain, oncology and/or gastrointestinal disorders.

Examples of such disorders are asthma, allergic rhinitis, pulmonary, cough, cold, inflammation, chronic obstructive pulmonary disease, airway reactivity, urticaria,hypertension, rheumatoid arthritis, edema, angiogenesis, pain, migraine, tension headache, psychoses, depression, anxiety, Alzheimer's disease, schizophrenia, Huntington's disease, bladder hypermotility, urinary incontinence, eating disorder, manic depression, substance dependence, movement disorder, cognitive disorder, obesity, stress disorders, micturition disorders, mania, hypomania and aggression, bipolar disorder, cancer, carcinoma, fibromyalgia, non cardiac chest pain, gastrointestinal hypermotility, gastric asthma, Crohn's disease, gastric emptying disorders, ulcerative colitis, irritable bowel syndrome, inflammatory bowel disease, emesis, gastric asthma, gastric motility disorders or gastro-esophageal reflux disease (GERD).

PHARMACOLOGY

Transfection and culturing of cells used in FLIPR and Binding assays

Chinese Hamster Ovary (CHO) K1 cells (obtained from ATCC) were stably transfected with the human NK_2 receptor (hNK_2R cDNA in pRc/CMV, Invitrogen) or the human NK_3 receptor (hNK_3R in pcDNA 3.1/Hygro (+)/IRES/CD8, Invitrogen vector modified at AstraZeneca EST-Bio UK, Alderley Park). The cells were transfected with the cationic lipid reagent LIPOFECTAMINE™ (Invitrogen) and selection was performed with Geneticin (G418, Invitrogen) at 1mg/ml for the hNK_2R transfected cells and with Hygromycin (Invitrogen) at 500μg/ml for the hNK_3R transfected cells. Single cell clones were collected by aid of Fluorescence Activated Cell Sorter (FACS), tested for functionality in a FLIPR assay (see below), expanded in culture and cryopreserved for future use. CHO cells stably transfected with human NK_1 receptors originates from AstraZeneca R&D, Wilmington USA. Human NK_1 receptor cDNA (obtained from RNA-PCR from lung tissue) was subcloned into pRcCMV (Invitrogen). Transfection was performed by Calcium Phosphate and selection with 1mg/ml G418.

The CHO cells stably transfected with hNK_1R, hNK_2R and hNK_3R were cultured in a humidified incubator under 5% CO_2, in Nut Mix F12 (HAM) with Glutamax I, 10% Foetal Bovine Serum (FBS), 1% Penicillin/Streptomycin (PEST) supplemented with 200μg/ml Geneticin for the hNK_1R and hNK_2R expressing cells and 500μg/ml Hygromycin for the hNK_3R expressing cells. The cells were grown in T175 flasks and routinely passaged when 70-80% confluent for up to 20-25 passages.

Assessing the Activity of Selected test Compounds to Inhibit Human $NK_1/NK_2/NK_3$ Receptor Activation (FLIPR assay)

The activity of a compound of the invention to inhibit $NK_1/NK_2/NK_3$ receptor activation measured as $NK_1/NK_2/NK_3$ receptor mediated increase in intracellular Ca^{2+} was assessed by the following procedure:

CHO cells stably transfected with human NK_1, NK_2 or NK_3 receptors were plated in black walled/clear bottomed 96-well plates (Costar 3904) at $3.5x10^4$ cells per well and grown for approximately 24h in normal growth media in a 37°C CO_2-incubator.

Before the FLIPR assay the cells of each 96-well plate were loaded with the Ca^{2+} sensitive dye Fluo-3 (TEFLABS 0116) at 4μM in a loading media consisting of Nut Mix F12 (HAM) with Glutamax I, 22mM HEPES, 2.5mM Probenicid (Sigma P-8761) and 0.04% Pluronic F-127 (Sigma P-2443) for 1 h kept dark in a 37°C CO_2-incubator. The cells were then washed three times in assay buffer (Hanks balanced salt solution (HBSS) containing 20mM HEPES, 2.5mM Probenicid and 0.1% BSA) using a multi-channel pipette leaving them in 150μl at the end of the last wash. Serial dilutions of a test compound in assay buffer (final DMSO concentration kept below 1%) were automatically pipetted by FLIPR (Fluorometric Imaging Plate Reader) into each test well and the fluorescence intensity was recorded (excitation 488 nm and emission 530 nm) by the FLIPR CCD camera for a 2 min pre-incubation period. 50μl of the Substance P (NK_1 specific), NKA (NK_2 specific), or Pro-7-NKB (NK_3 specific) agonist solution (final concentration equivalent to an approximate EC_{60} concentration) was then added by FLIPR into each well already containing 200μl assay buffer (containing the test compound or vehicle) and the fluorescence was continuously monitored for another 2 min. The response was measured as the peak relative fluorescence after agonist addition and IC_{50}s were calculated from ten-point concentration-response curves for each compound. The IC_{50}s were then converted to pK_B values with the following formula:

$K_B = IC_{50} / 1+ (EC_{60}$ conc. of agonist used in assay / EC_{50} agonist)

$pK_B = - \log K_B$

Determining the Dissociation Constant (Ki) of compounds for Human NK_1/NK_2/NK_3 Receptors (Binding Assay)

Membranes were prepared from CHO cells stably transfected with human NK_1, NK_2 or NK_3 receptors according to the following method.

Cells were detached with Accutase® solution, harvested in PBS containing 5% FBS by centrifugation, washed twice in PBS and resuspended to a concentration of $1x10^8$ cells/ml

in Tris-HCl 50 mM, KCl 300 mM, EDTA-N_2 10 mM pH 7.4 (4°C). Cell suspensions were homogenized with an UltraTurrax 30 s 12.000 rpm. The homogenates were centrifuged at 38.000 x g (4°C) and the pellet resuspended in Tris-HCl 50 mM pH 7.4. The homogenization was repeated once and the homogenates were incubated on ice for 45 min. The homogenates were again centrifuged as described above and resuspended in Tris-HCl 50mM pH 7.4. This centrifugation step was repeated 3 times in total. After the last centrifugation step the pellet was resuspended in Tris-HCl 50mM and homogenized with Dual Potter, 10 strokes to a homogenous solution, an aliquot was removed for protein determination. Membranes were aliquoted and frozen at -80°C until use.

The radioligand binding assay is performed at room temperature in 96-well microtiter plates (No-binding Surface Plates, Corning 3600) with a final assay volume of 200µl/well in incubation buffer (50mM Tris buffer (pH 7.4 RT) containing 0.1 % BSA, 40 mg/L Bacitracin, complete EDTA-free protease inhibitor cocktail tablets 20 pills/L (Roche) and 3mM $MnCl_2$). Competition binding curves were done by adding increasing amounts of the test compound. Test compounds were dissolved and serially diluted in DMSO, final DMSO concentration 1.5 % in the assay. 50µl Non labelled ZD 6021 (a non selective NK-antagonist, 10µM final conc) was added for measurement of *non-specific binding*. For *total binding*, 50µl of 1.5% DMSO (final conc) in incubation buffer was used.[^{3}H-Sar,Met(O_2)-Substance P] (4nM final conc) was used in binding experiments on hNK_1r. [^{3}H-SR48968] (3nM final conc.) for hNK_2r and [^{3}H-SR142801] (3nM final conc) for binding experiments on hNK_3r. 50µl radioligand, 3µl test compound diluted in DMSO and 47µl incubation buffer were mixed with 5-10µg cell membranes in 100µl incubation buffer and incubated for 30 min at room temperature on a microplate shaker.

The membranes were then collected by rapid filtration on Filtermat B(Wallac), presoaked in 0.1% BSA and 0.3% Polyethyleneimine (Sigma P-3143), using a Micro 96 Harvester (Skatron Instruments, Norway). Filters were washed by the harvester with ice-cold wash buffer (50mM Tris-HCl, pH 7.4 at 4°C, containing 3mM $MnCl_2$) and dried at 50°C for 30-60 min. Meltilex scintillator sheets were melted on to filters using a Microsealer (Wallac, Finland) and the filters were counted in a β-Liquid Scintillation Counter (1450 Microbeta, Wallac, Finland).

The K_i value for the unlabeled ligand was calculated using the Cheng-Prusoff equation (Biochem. Pharmacol. 22:3099-3108, 1973): where L is the concentration of the radioactive ligand used and K_d is the affinity of the radioactive ligand for the receptor, determined by saturation binding.

Data was fitted to a four-parameter equation using Excel Fit.

$K_i = IC_{50} / (1+(L/K_d))$

Results

In general, the compounds of the invention, which were tested, demonstrated statistically significant antagonistic activity at the NK_1 receptor within the interval 7-9 for the pK_B. For the NK_2 receptor the interval for the pK_B was 7-9. In general, the antagonistic activity at the NK_3 receptor was less than 7.5 for the pK_B.

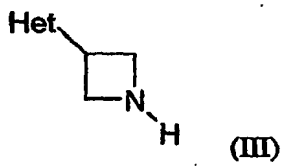
In general, the compounds of the invention, which were tested, demonstrated statistically significant CYP3A4 inhibition at a low level. The IC_{50} values tested according to Bapiro et al; Drug Metab. Dispos. 29, 30-35 (2001) were generally greater than 2 μM.

Thus, the tested compounds according to the invention have been shown to be selective and dual NK_1/ NK_2 receptor antagonists as well as showing low levels of CYP3A4 inhibition.

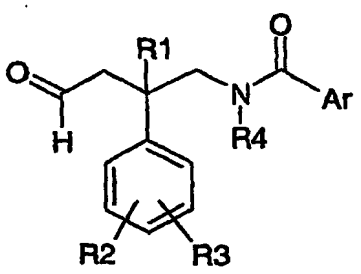
Methods of Preparation

In another aspect the present invention provides a process for preparing a compound of the formula (I) or salts thereof which process comprises:

a) reacting a compound of the formula (III) with a compound of the formula (IV):



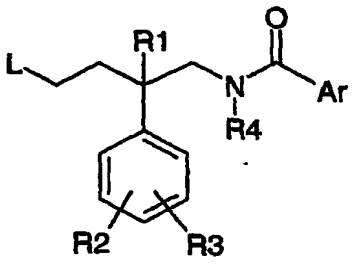
(III)



(IV)

wherein R1-R4, Het, and Ar are as hereinbefore defined; and the conditions are such that reductive alkylation of the compounds of the formulae (III) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formulae (III) and the carbon atom of the aldehyde group of the compounds of formulae (IV); or

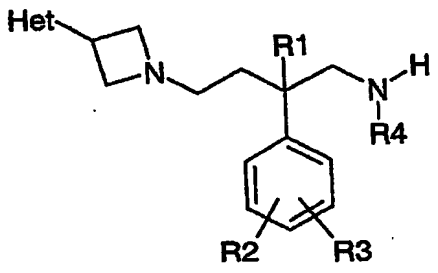
b) reacting a compound of the formula (III) with a compound of the formula (V):



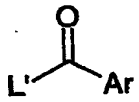
(V)

wherein R1-R4, Het, and Ar are as hereinbefore defined; and L is a group such that alkylation of the compounds of the formulae (III) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formulae (III) and the carbon atom of the compounds of formulae (V) that is adjacent to the L group; or

c) reacting a compound of the formula (VI) with a compound of the formula (VII):



(VI)



(VII)

wherein R1-R4, Het and Ar are as hereinbefore defined; and L' is a leaving group; wherein any other functional group is protected, if necessary, and:

i) removing any protecting groups;

ii) optionally oxidizing any oxidizeable atoms;

iii) optionally forming a pharmaceutically acceptable salt.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question, and may be introduced and removed by conventional methods; see for example Protecting Groups in Organic Chemistry; Theodora W. Greene. Methods of removal are chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

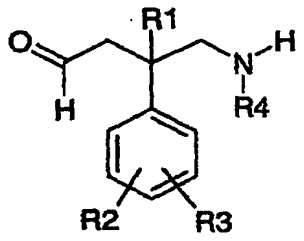
It will also be appreciated that certain of the various optional substituents in the compounds of the formula (I) may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes described hereinabove. The reagents and reaction conditions for such procedures are well known in the chemical art.

The compounds of the formulae (III) and (IV) are reacted under conditions of reductive alkylation. The reaction is typically performed at a non-extreme temperature, for example

0 - 100 °C, in a substantially inert solvent for example dichloromethane. Typical reducing agents include borohydrides such as sodium cyanoborohydride.

The compounds of the formulae (III) and (V) are reacted under conditions of alkylation. Typically in the compounds of the formula (V) L is a leaving group such as halo or alkylsulfonyloxy. The reaction is typically performed at an elevated temperature, for example 30 - 130 °C, in a substantially inert solvent for example DMF.

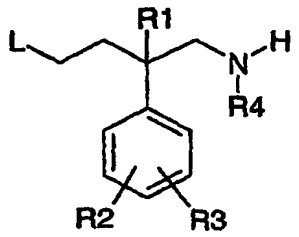
The compounds of the formula (III) are known or may be prepared in conventional manner. The compounds of the formula (IV) may be prepared, for example, by reacting a compound of the formula (VII) with a compound of the formula (VIII):



(VIII)

wherein R1-R4 are as hereinbefore defined under conventional acylation conditions.

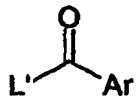
The compounds of the formula (V) may be prepared, for example, by reacting a compound of the formula (VII) with a compound of the formula (IX):



(IX)

wherein R1-R4 and L are as hereinbefore defined under conventional acylation conditions.

The compounds of the formulae (VI) and (VII) may be reacted under conventional acylation conditions wherein



is an acid or an activated acid derivative. Such activated acid derivatives are well known in the literature. They may be formed in situ from the acid or they may be prepared, isolated and subsequently reacted. Typically L' is chloro thereby forming the acid chloride. Typically the acylation reaction is performed in the presence of a non-nucleophilic base, for example N,N-diisopropylethylamine, in a substantially inert solvent such as dichloromethane at a non-extreme temperature.

The compounds of the formula (VIII) and (IX) are known or may be prepared in conventional manner.

Certain compounds of the formulae (III), (IV), (V), (VI), (VII), (VIII) and (IX) are novel and form part of the present invention.

Thus, another aspect of the invention is the intermediates *tert*-butyl [(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate,

[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine,

[(2*S*)-2-(3,4-dichlorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl]methylamine,

1-[1-(diphenylmethyl)azetidin-3-yl]pyrrolidin-3-ol,

8-[1-(diphenylmethyl)azetidin-3-yl]-1,4-dioxa-8-azaspiro[4.5]decane,

8-azetidin-3-yl-1,4-dioxa-8-azaspiro[4.5]decane,

3-cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-hydroxyazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide,

3-cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-hydroxyazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide,

tert-butyl [2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate,

[2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine,

ethyl 5-cyano-1-benzothiophene-7-carboxylate,

5-cyano-1-benzothiophene-7-carboxylic acid,

3-cyano-*N*-[2-(4-fluorophenyl)pent-4-en-1-yl]-*N*-methyl-1-naphthamide,

3-cyano-*N*-[2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide,

{2-(4-bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylamine,

tert-butyl {2-(4-bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate,

tert-butyl {2-(4-cyanophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate,

4-{3-hydroxy-1-[(methylamino)methyl]propyl}benzonitrile,

3-cyano-*N*-[2-(4-cyanophenyl)-4-hydroxybutyl]-*N*-methyl-1-naphthamide,

3-cyano-*N*-[2-(4-cyanophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide,

tert-butyl [2-(4-fluorophenyl)pent-4-en-1-yl]methylcarbamate,

1-[(*tert*-butoxycarbonyl)(methyl)amino]-1,2,3-trideoxy-2-(4-fluorophenyl)pentitol,

tert-butyl [2-(4-fluorophenyl)-4-oxobutyl]methylcarbamate, and

7-chloro-2,3-dihydro-1,4-benzodioxine-5-carbaldehyde

as a free base or any salt thereof.

Working Examples

It should be emphasised that the compounds of the present invention most often show highly complex NMR spectra due to the existence of conformational isomers. This is believed to be a result from slow rotation about the amide and/or aryl bond. The following abbreviations are used in the presentation of the NMR data of the compounds: s-singlet; d-doublet; t-triplet; qt-quartet; qn-quintet; m-multiplet; b-broad; cm-complex multiplet, which may include broad peaks.

The following examples will describe, but not limit, the invention. SM in the tables is Starting Material.

Example 1

3,5-Dichloro-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methylbenzamide acetate

[(2*S*)-2-(3,4-Dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine hydrochloride (Method 40; 89 mg, 0.21 mmol) was dissolved in DMF (2 mL) and to the resultant solution were added 3,5-dichlorobenzoic acid (44 mg, 0.23 mmol), TBTU (80

mg, 0.25 mmol) and DIPEA (108 mg, 0.84 mmol) in the given order. The solution was stirred at RT for 1.5 h, diluted with water and then neutralized by the addition of $NaHCO_3$. The mixture was extracted twice with ethyl acetate and the combined organic solutions were dried over $MgSO_4$. The solvent was removed by evaporation to yield 79 mg of crude product. The product was purified by reversed phase chromatography using a mixture of acetonitrile and 0.1 M ammonium acetate aq. There was obtained 43 mg (37%) of the title compound as a white solid. ^1H NMR (500 MHz, CD_3CN): 1.3-1.8 (cm, 3H), 2.0-4.6 (cm, 24H), 6.8-8.0 (cm, 6H); MS: m/z 562 (M^+).

Examples 2-11

The following compounds were synthesised in an analogous method to Example 1.

Ex	Compound	^1H NMR	m/z	Yield	SM
2	*N*-{(2*S*)-2-(3,4-Dichlorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-2-methoxy-*N*-methylquinoline-4-carboxamide		589	5%	Meth 41 *(and J Med Chem; 1992; 4893)*
3	*N*-[(2S)-2-(3,4-Dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-3,5-difluoro-*N*-methylbenzamide acetate	(300 MHz, CD_3OD): 1.6-2.0 (cm, 3H), 2.0 (s, 3H), 2.4-4.0 (cm, 20H), 6.4-7.6 (cm, 6H)	528	75%	Meth 40
4	*N*-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-3,5-bis(trifluoromethyl)benzamide acetate	(300 MHz, CD_3OD): 1.5-2.4 (cm, 3H), 2.0 (s, 3H), 2.4-4.0 (cm, 20H), 6.9-7.7 (cm, 5H), 8.0 (s, 1H)	628	52%	Meth 40
5	5-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-	(300 MHz, CD_3OD): 1.4-2.2 (cm, 3H), 2.0 (s,	573	56%	Meth 40

	thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-1-benzothiophene-7-carboxamide acetate	3H), 2.4-4.0 (cm, 20H), 6.7-7.8 (cm, 4H), 7.5 (d, 1H), 7.8 (d, 1H), 8.3 (s, 1H)			42
6	3-Cyano-*N*-[(2S)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methylbenzamide acetate	(300 MHz, CD_3OD): 1.4-2.4 (cm, 3H), 2.0 (s, 3H), 2.4-3.8 (cm, 20H), 6.9-7.6 (cm, 6H), 7.8 (d, 1H)	517	79%	Meth 40
7	3-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide acetate	(400 MHz, $CDCl_3$): 1.4-4.4 (cm, 35H), 6.7-7.4 (cm, 4H), 7.4 (d, 1H)	571	36%	Meth 40 *(and WO 00/34243)*
8	2-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methylquinoline-4-carboxamide acetate	(400 MHz, $CDCl_3$): 1.4-2.0 (cm, 3H), 2.0 (s, 3H), 2.2-4.4 (cm, 20H), 6.4-7.9 (cm, 8H), 8.2 (d, 1H)	568	30%	Meth 40 *(and J Prakt Chem; 1902; 264)*
9	3-Cyano-*N*-[2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide diacetate	(400 MHz, $CDCl_3$): 1.4-2.0 (cm, 6H), 2.0 (s, 6H), 2.2-4.0 (cm, 19H), 6.74-7.4 (cm, 6H)	521	19%	Meth 50 *(and WO 00/34243)*
10	*N*-[2-(4-Fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-3,5-bis(trifluoromethyl)benzamide diacetate	(400 MHz, $CDCl_3$): 1.4-2.0 (cm, 2H), 2.0 (s, 6H), 2.2-3.8 (cm, 21H), 6.8-7.6 (cm, 6H), 7.8 (s, 1H)	578	17%	Meth 50

11	7-Chloro-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-2,3-dihydro-1,4-benzodioxine-5-carboxamide acetate	(400 MHz, CD_3OD): 1.4-2.0 (cm, 2H), 2.0 (s, 3H), 2.4-4.4 (cm, 25H), 6.4-7.6 (cm, 5H)	584	11%	Meth 40 52

Example 12

3-Cyano-*N*-{(2*S*)-2-(3,4-dichlorophenyl)-4-[3-(3-hydroxypyrrolidin-1-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide acetate

3-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide (*WO 00/02859*; 38 mg, 0.089 mmol) was dissolved in CH_2Cl_2 (3 mL) and to the resultant solution was added 1-azetidin-3-ylpyrrolidin-3-ol dihydrochloride (Method 43; 20 mg, 0.093 mmol) dissolved in a few drops of methanol. Sodium triacetoxyborohydride (25 mg, 0.118 mmol) was added and the solution was stirred at room temperature over night. The mixture was diluted with CH_2Cl_2, washed with brine and then dried over $MgSO_4$. The solvent was removed by evaporation and the residue chromatographed on a reversed phase column using a mixture of acetonitrile and 0.1 M ammonium acetate aq. There was obtained 19 mg (35%) of the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD): 0.8-4.9 (cm, 25H), 6.4-7.9 (cm, 7H), 7.9-8.1 (m, 1H), 8.4 (s, 1H); MS: m/z 551 (M^+).

Examples 13-19

The following compounds were synthesised in an analogous method to Example 11.

Ex	Compound	^{1}H NMR	m/z	Yield	SM
13	3-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide acetate	(500 MHz, $CDCl_3$): 1.2-2.2 (cm, 3H), 2.0 (s, 3H), 2.2-5.0 (cm, 21H), 6.5-7.0 (cm, 1H), 7.2-8.0 (cm, 7H), 8.2 (d, 1H)	551	35%	*(WO 00/2859 and WO 00/63168)*
14	3-Cyano-*N*-[(2*S*)-2-(3,4-	(400 MHz, DMSO-d_6):	567	51%	Meth

	dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide acetate	1.2-2.2 (cm, 3H), 1.90 (s, 3H), 2.3-4.5 (cm, 21H), 6.4-7.3 (cm, 2H), 7.4 (dd, 1H), 7.5-7.8 (cm, 4H), 8.0-8.2 (m, 1H), 8.6 (d, 1H)			40 *(and WO 00/02859)*
15	3-Cyano-*N*-{(2*S*)-2-(3,4-dichlorophenyl)-4-[3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide diacetate	(400 MHz, CD_3OD): 1.4-2.0 (cm, 3H), 1.6-1.8 (m, 4H), 1.9 (s, 6H), 2.3-4.0 (cm, 20H), 6.4-7.2 (m, 2H), 7.4-7.8 (m, 5H), 8.0-8.1 (m, 1H), 8.4 (d, 1H)	607	78%	Meth 44 *(and WO 00/02859)*
16	3-Cyano-*N*-{(2*S*)-2-(3,4-dichlorophenyl)-4-[3-(4-hydroxypiperidin-1-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide diacetate	(400 MHz, CD_3OD): 1.4-2.4 (cm, 16H), 2.5-2.9 (cm, 5H), 3.0-4.1 (cm, 9H), 6.5-7.8 (cm, 7H), 8.0-8.1 (m, 1H), 8.4 (d, 1H)	565	14%	Meth 49 *(and WO 00/02859)*
17	3-Cyano-*N*-[2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide	(400 MHz, $CDCl_3$): 1.4-3.5 (cm, 22H), 3.8-4.4 (cm, 1H), 6.4-8.0 (cm, 8H), 8.2 (s, 1H)	517	94%	Meth 40 46
18	3-Cyano-*N*-[2-(4-cyanophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide acetate	(400 MHz, $CDCl_3$): 1.2-2.2 (cm, 3H), 2.1 (s, 3H), 2.4-4.4 (cm, 20H), 6.6-7.8 (cm, 7H), 7.9 (d, 1H), 8.2 (s, 1H)	524	52%	Meth 40 47
19	3-Cyano-*N*-{(2*S*)-2-(3,4-dichlorophenyl)-4-[3-(1,1-	(400 MHz, DMSO-d_6): 1.2-1.9 (cm, 3H), 1.9 (s,	599	39%	Meth 48

	dioxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide acetate	3H), 2.0-4.8 (cm, 20H), 6.4-7.8 (cm, 7H), 8.0-8.2 (m, 1H), 8.6 (d, 1H)			*(and WO 00/02859)*

Example 20

3-Cyano-*N*-{(2S)-2-(3,4-dichlorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide diacetate

3-Cyano-*N*-[(2S)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide acetate (Example 14; 127 mg, 0.20 mmol) was dissolved in acetic acid (10 mL) and to the resultant solution was added hydrogen peroxide (0.04 mL of 30% aqueous solution, 0.35 mmol). The mixture was stirred at room temperature for 3 days then diluted with water. The solvent was removed by lyophilising the mixture to give a residue, which was purified by reversed phase chromatography using a mixture of acetonitrile and 0.1 M ammonium acetate aq. There was obtained 52 mg (35%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.2-2.2 (m, 3H), 1.9 (s, 3H), 2.3-3.6 (m, 20H), 4.4 (c m, 1H), 6.4-7.6 (m, 2H), 7.4 (dd, 1H), 7.6-8.2 (5H), 8.6 (d, 1H); MS: m/z 583 (M^+).

Example 21

3-Cyano-*N*-{2-(4-cyanophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide acetate

3-Cyano-*N*-[2-(4-cyanophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide acetate (Example 18; 60 mg, 0.10 mmol) was dissolved in a mixture of acetonitrile (3 mL) and CH_2Cl_2 (1 mL) and to the resultant solution was added a catalytic amount of $FeCl_3$ with cooling. The mixture was stirred for 5 min and then periodic acid (26 mg, 0.11 mmol) was added whereupon stirring was continued overnight at 0°C. Another catalytic amount of $FeCl_3$ as well as an additional portion of periodic acid (26 mg, 0.11 mmol) was added. The reaction mixture was stirred at 0°C for 2 h and then quenched by addition of $Na_2S_2O_3$. The mixture was extracted trice with CH_2Cl_2 and the organics washed twice with water and then dried over Na_2SO_4. The solvent was removed by evaporation and the product was purified by reversed phase chromatography using a mixture of acetonitrile and 0.1 M ammonium acetate aq. There was obtained 25 mg (41%)

of the title compound as a pale yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$): 1.4-2.0 (cm, 3H), 2.0 (s, 3H), 2.1-4.3 (cm, 20H), 6.4-8.0 (cm, 9H), 8.2 (s, 1H); MS: m/z 540 (M^+).

Examples 22-27

The following compounds were synthesised in an analogous method to Example 21.

Ex	Compound	^{1}H NMR	m/z	Yield	SM
22	3,5-Dichloro-*N*-{(2*S*)-2-(3,4-dichlorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methylbenzamide acetate	(300 MHz, CD_3OD): 1.6 (b, 1H), 1.8 (b, 1H), 2.0 (s, 3H), 2.2-3.8 (cm, 21H), 6.8-7.6 (cm, 6H)	576	1%	Ex 1
23	*N*-[(2S)-2-(3,4-Dichlorophenyl)-4-(3-oxidothiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-3,5-bis(trifluoromethyl)benzamide acetate	(300 MHz, CD_3OD): 1.5-2.0 (cm, 2H), 2.0 (s, 3H), 2.2-4.0 (cm, 18H), 6.8-7.8 (cm, 5H), 8.1 (s, 1H)	644	9%	Ex 4
24	3-Cyano-*N*-{(2*S*)-2-(3,4-dichlorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide acetate	(400 MHz, $CDCl_3$): 1.4-4.4 (cm, 35H), 6.7-7.2 (cm, 2H), 7.3 (s, 1H), 7.4 (s, 1H), 7.5 (d, 1H)	587	37%	Ex 7
25	3-Cyano-*N*-{2-(4-fluorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide acetate	(400 MHz, $CDCl_3$): 1.4-2.0 (cm, 3H), 2.0 (s, 3H), 2.1-4.3 (cm, 20H), 6.4-8.0 (cm, 9H), 8.2 (s, 1H)	533	42%	Ex 17

26	3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide acetate	(400 MHz, $CDCl_3$): 1.4-2.0 (cm, 6H), 2.0 (s, 3H), 2.1-4.0 (cm, 25H), 6.9-7.4 (cm, 6H)	537	38%	Ex 9
27	*N*-{2-(4-Fluorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-3,5-bis(trifluoromethyl)benzamide acetate	(400 MHz, $CDCl_3$): 1.4-2.0 (cm, 3H), 2.0 (s, 3H), 2.1-4.4 (cm, 21H), 6.7-7.4 (cm, 5H), 7.5 (s, 1H), 8.2 (s, 1H)	594	47%	Ex 10

Example 28

3-Cyano-N-{(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-oxopiperidin-1-yl)azetidin-1-yl]butyl}-N-methyl-1-naphthamide diacetate

3-cyano-*N*-{(2S)-2-(3,4-dichlorophenyl)-4-[3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide diacetate (Example 15; 35 mg, 0.058 mmol) was dissolved in a few drops of acetone-water (1:1) and to the resultant solution was added pyridinium *p*-toluenesulfonate (43 mg, 0.17 mmol). The mixture was subjected to microwave single node heating for 10 min and then the solvent was removed by evaporation. The residue was dissolved in CH_2Cl_2 and the solution was washed with $NaHCO_3$ aq. then dried over $MgSO_4$. Removal of solvent by evaporation yielded an oil, which was purified by reversed phase chromatography using a mixture of acetonitrile and 0.1 M ammonium acetate aq. There was obtained 35 mg (89%) of the title compound as a white solid. ^1H NMR (400 MHz, CD_3OD): 1.4-2.2 (cm, 3H), 1.9 (s, 6H), 2.3-4.0 (cm, 20H), 6.4-7.8 (cm, 7H), 8.0-8.2 (cm, 1H), 8.6 (d, 1H); MS: m/z 563 (M^+).

Example 29

3-Cyano-N-{(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-fluoropiperidin-1-yl)azetidin-1-yl]butyl}-N-methyl-1-naphthamide

Diethylaminosulfur trifuoride (7 mg, 0.044 mmol) was dissolved in dry CH_2Cl_2 and cooled with stirring under argon to –65°C. 3-Cyano-N-{(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-oxopiperidin-1-yl)azetidin-1-yl]butyl}-N-methyl-1-naphthamide (Example 16; 40 mg, 0.071 mmol), which was dissolved in dry CH_2Cl_2 (0.5 mL), was then added. The external cooling was removed and the solution was stirred for 1 h. The reaction mixture was quenched by dropping it to a saturated solution of $NaHCO_3$ aq. (6 mL). The organic solution was washed with water and then dried over $MgSO_4$. The solvent was removed by evaporation and there was obtained 5 mg (12%) of the title compound as an oil. ^{1}H NMR (500 MHz, CD_3OD): 1.8-2.6 (cm, 7H), 2.6-3.3 (cm, 7H), 3.4-4.4 (cm, 9H), 5.0-5.3 (cm, 1H), 7.0-8.4 (cm, 7H), 8.4-8.6 (m, 1H), 8.9-9.0 (d, 1H); MS: m/z 567 (M^+).

Example 30

3-Cyano-N-[(2S)-2-(3,4-dichlorophenyl)-4-(3-piperidin-1-ylazetidin-1-yl)butyl]-N-methyl-1-naphthamide acetate

1-[(3*S*)-4-[(3-Cyano-1-naphthoyl)(methyl)amino]-3-(3,4-dichlorophenyl)butyl]azetidin-3-yl methanesulfonate (Method 45; 87 mg, 0.16 mmol) and 1-methylpiperazine (1 mL, 9.0 mmol) were dissolved in CH_2Cl_2 (1.5 mL) and the resultant mixture was subjected to microwave single node heating for 5 minutes. The solvent was removed by evaporation and the product was purified by reversed phase chromatography using a mixture of acetonitrile and 0.1 M ammonium acetate aq. There was obtained 5 mg (5%) of the title compound as a white solid. ^{1}H NMR: (500 MHz, CD_3OD): 1.2-4.0 (cm, 29H), 6.5-8.0 (cm, 8H), 8.4 (d, 1H); MS: m/z 564 (M^+).

Examples 31-32

The following compounds were synthesised in an analogous method to Example 30.

Ex	Compound	^{1}H NMR	m/z	Yield	SM
31	*N*-[(2*S*)-4-[3-(4-Acetylpiperazin-1-yl)azetidin-	(500 MHz, CD_3OD): 1.2-3.8 (cm, 29H), 6.4-	592	3%	Meth 45

	1-yl]-2-(3,4-dichlorophenyl)butyl]-3-cyano-*N*-methyl-1-naphthamide acetate	7.8 (cm, 7H), 7.9-8.0 (m, 1H), 8.3-8.4 (d, 1H)			
32	3-Cyano-*N*-[(2*S*)-4-[3-(4-cyanopiperidin-1-yl)azetidin-1-yl]-2-(3,4-dichlorophenyl)butyl]-*N*-methyl-1-naphthamide acetate		3%	574	Meth 45

Preparation of Starting Materials

The starting materials for the examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials.

Method 40

[(2*S*)-2-(3,4-Dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine hydrochloride

(a) *4-[1-(Diphenylmethyl)azetidin-3-yl]thiomorpholine*

A mixture of 1-(Diphenylmethyl)azetidin-3-yl methanesulfonate (*J. Org. Chem.; 56; 1991; 6729*; 10 g, 31.5 mmol), thiomorpholine (3.9 g, 38 mmol) and DIPEA (4.9 g, 38 mmol) was refluxed overnight. The volatiles were removed by evaporation and the residue was partitioned between CH_2Cl_2 and $NaHCO_3$ aq. The organic layer was washed twice with $NaHCO_3$ aq. and then extracted with an aqueous solution of citric acid (3x70 mL of 1M). The aqueous layer was cooled and then pH adjusted with aqueous $NaHCO_3$ and then 2M NaOH aq. The mixture was extracted with a mixture of CH_2Cl_2-EtOAc-ethanol and the organic solution was dried over $MgSO_4$ and then removed by evaporation. There was obtained 9.3 g (91%) of 4-[1-(diphenylmethyl)azetidin-3-yl]thiomorpholine as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$): 2.5 (m, 4H), 2.7 (m, 4H), 2.8 (t, 2H), 3.0 (qn, 1H), 3.4 (m, 2H), 4.4 (s, 1H), 7.1-7.4 (m, 10H); MS: m/z 325 (M^+).

(b) *4-Azetidin-3-ylthiomorpholine dihydrochloride*

4-[1-(Diphenylmethyl)azetidin-3-yl]thiomorpholine (1.0 g, 3.1 mmol) was dissolved in CH_2Cl_2 under nitrogen and stirred at 0°C during the addition of 1-chloroethyl chloroformate (1.3 g, 9.2 mmol). The mixture was stirred for 90 min and then methanol (1 mL) was added. The solution was refluxed for 20 min and the solvent was removed by evaporation. To the residue was added acetone (10 mL) followed by isopropanol (10 mL) and the mixture was then refluxed for 30 min and then placed at RT overnight. The mixture was cooled and the precipitate was collected by filtration. There was obtained 250 mg (51%) of 4-azetidin-3-ylthiomorpholine dihydrochloride as a pale brown solid. ^1H NMR (400 MHz, DMSO-d_6): 2.4-3.8 (c m, 8H), 4.0 (b, 2H), 4.3 (m, 1H), 4.5 (b, 2H) 9.2 (b, 1H), 10.4 (b, 1H).

(c) *tert-Butyl [(2S)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate*

tert-Butyl [(2*S*)-2-(3,4-dichlorophenyl)-4-oxobutyl]methylcarbamate (610 mg, 1.8 mmol) was dissolved in 1,2-dichloroethane (20 mL) and to the resultant solution was added 4-azetidin-3-ylthiomorpholine hydrochloride (430 mg, 1.9 mmol) followed by the addition of sodium triacetoxyborohydride (480 mg, 2.2 mmol). The mixture was stirred at room temperature for 5 h and then triethylamine (0.73 mL, 5.2 mmol) was added. The reaction mixture was stirred for 2 h and then partitioned between CH_2Cl_2 and $NaHCO_3$ aq. The organic layer was washed with water and the combined organic solutions were dried over $MgSO_4$. The solvent was removed by evaporation to yield an oil, which was chromatographed on a reversed phase column using a mixture of acetonitrile and 0.1 M ammonium acetate aq. The appropriate fractions were extracted with ether. The organic solution was dried over $MgSO_4$ and then the solvent was removed by evaporation. There was obtained 266 mg (31%) of *tert*-butyl [(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate as an oil. ^1H NMR (400 MHz, $CDCl_3$): 1.4 (s, 9H), 1.5-3.5 (c m, 23H), 7.0 (dd, 1H), 7.3 (d, 1H), 7.4 (d, 1H); MS: m/z 488 (M^+).

(d) *[(2S)-2-(3,4-Dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine hydrochloride*

tert-Butyl [(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate (260 mg, 0.53 mmol) was dissolved in ether (15 mL) and stirred during the dropwise addition of HCl (15 mL of 4M dioxane solution). The mixture was stirred at room temperature for 1 h and then the solvent was removed by evaporation. There was obtained 270 mg (100%) of [(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine hydrochloride as a white solid. ^{1}H NMR (300 MHz, CD_3OD): 1.9-2.2 (b, 2H), 2.7 (s, 3H), 3.0-4.8 (cm, 19H), 7.4 (d, 1H), 7.6 (m, 2H); MS: m/z 388 (M^+).

Method 41

{(2*S*)-2-(3,4-Dichlorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}methylamine diacetate

[(2*S*)-2-(3,4-Dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine hydrochloride (Method 40; 270 mg, 0.54 mmol) was dissolved in acetic acid and to the resultant solution was added hydrogen peroxide (0.05 mL of 35% aqueous solution, 0.54 mmol). The mixture was stirred at room temperature for 2.5 h and the solvent was removed by evaporation. The residue was dissolved in ethanol (50 mL) and to the resultant solution was added MP-Carbonate resin (0.86 g of 3.18 mmol/g polymer-bound resin). The mixture was stirred for 30 min and then filtered whereupon the solvent was removed by evaporation. The product was purified by reversed phase chromatography using a mixture of acetonitrile and 0.1 M ammonium acetate aq. There was obtained 140 mg (49%) of {(2*S*)-2-(3,4-Dichlorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}methylamine diacetate. ^{1}H NMR (400 MHz, $CDCl_3$): 1.6-1.8 (m, 2H), 1.9 (s, 6H), 2.3-2.4 (m, 1H), 2.4-2.5 (m, 7H), 2.7-3.0 (m, 10H), 3.1 (m, 1H), 3.6 (m, 2H), 7.0 (dd, 1H), 7.2 (d, 1H), 7.3 (d, 1H), 8.2 (s, 2H); MS: m/z 404 (M^+).

Method 42

5-Cyano-1-benzothiophene-7-carboxylic acid

(a) *Ethyl 5-cyano-1-benzothiophene-7-carboxylate*

N-[2-cyano-3-(dimethylamino)prop-2-en-1-ylidene]-*N*-methylmethanaminium perchlorate (*Collect. Czech. Chem. Commun.; 32; 5; 1967; 1704*; 5.84 g, 23.2 mmol) and ethyl 2-thienylacetate (3.95 g, 23.2 mmol) were mixed with quinoline (117 mL) at 0°C. Sodium ethoxide (1.97 g,

27.9 mmol) was added and the mixture was stirred at 0°C for 30 min and then at RT for 15 min. The reaction mixture was heated to 75°C under nitrogen for 5 h and then cooled to 0°C. Hydrochloric acid (200 mL of 2N aqueous solution) was added and the mixture extracted trice with chloroform. The organic solution was washed with brine and then dried over Na_2SO_4. The solvent was removed by evaporation and the residue flash chromatographed on silica gel (hexane-ethyl acetate, 8:1). There was obtained 2.3 g (43%) of ethyl 5-cyano-1-benzothiophene-7-carboxylate as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): 1.5 (t, 3H), 4.5 (qt, 2H), 7.5 (d, 1H), 7.7 (d, 1H), 8.3 (m, 2H).

(b) *5-Cyano-1-benzothiophene-7-carboxylic acid*

Ethyl 5-cyano-1-benzothiophene-7-carboxylate (5.6 g, 24.3 mmol) was dissolved THF (96 mL) and to the resultant solution was added an aqueous solution of NaOH (1.07 g of NaOH in 14 mL of water, 26.7 mmol) at 0°C. The mixture was stirred at RT overnight and then most of the solvent was removed by evaporation. The residue was dissolved in an aqueous solution of NaOH (0.1 M). The solution was washed trice with chloroform, acidified with 2M HCl and then extracted with ethyl acetate. The organic solution was evaporated and the residue flash chromatographed on silica gel (CH_2Cl_2-MeOH-NH_4OH, 8:2:0.5). There was obtained 4.3 g (85%) of 5-cyano-1-benzothiophene-7-carboxylic acid as a tan solid. ^{1}H NMR (500 MHz, DMSO-d_6): 7.7 (d, 1H), 8.1 (d, 2H), 8.3 (d, 1H), 8.7 (s, 1H), 14 (b, 1H); MS: m/z 202 (M^-).

Method 43

1-Azetidin-3-ylpyrrolidin-3-ol dihydrochloride

(a) *1-[1-(diphenylmethyl)azetidin-3-yl]pyrrolidin-3-ol*

1-(Diphenylmethyl)azetidin-3-yl methanesulfonate (*J. Org. Chem.; 56; 1991; 6729*; 310 mg, 0.98 mmol) was dissolved in acetonitrile (3.5 mL). Pyrrolidin-3-ol (104 mg, 1.2 mmol) and triethylamine (124 mg, 1.2 mmol) were added and the mixture was subjected to microwave single node heating for 10 minutes. The solvent was removed by evaporation and the residue was dissolved in ethyl acetate. The solution was washed with water and dried over $MgSO_4$ and then evaporated. There was obtained 280 mg (93%) of 1-[1-(diphenylmethyl)azetidin-3-yl]pyrrolidin-3-ol as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): 1.6-

1.8 (m, 1H), 2.1-2.3 (m, 2H), 2.4-2.6 (m, 2H), 2.6-2.8 (m, 1H), 2.9-3.0 (m, 2H), 3.1-3.2 (m, 1H), 3.3-3.4 (m, 2H), 4.3 (m, 1H), 4.4 (s, 1H), 7.1-7.5 (m, 10H); MS: m/z 309 (M^+).

(b) *1-Azetidin-3-ylpyrrolidin-3-ol*

1-[1-(diphenylmethyl)azetidin-3-yl]pyrrolidin-3-ol (310 mg, 0.98 mmol) was dissolved in ethanol (20 mL). A mixture of palladium hydroxide on carbon and palladium on activated carbon was added and to the resultant mixture was then added concentrated HCl (0.1 mL) dropwise. The mixture was stirred under hydrogen (5 atm) at RT overnight and then the catalyst was filtered off by means of Celite®. The solvent was removed by evaporation and the residue triturated with CH_2Cl_2. There was obtained 154 mg (79%) of 1-azetidin-3-ylpyrrolidin-3-ol dihydrochloride as a solid. ^{13}C NMR (75 MHz, D_2O): 48.8 (s), 65.1 (s), 67.7 (s), 70.9 (s), 76.2 (s), 85.7 (s); MS: m/z 143 (M^+).

Method 44

8-Azetidin-3-yl-1,4-dioxa-8-azaspiro[4.5]decane hydrochloride

(a) *8-[1-(diphenylmethyl)azetidin-3-yl]-1,4-dioxa-8-azaspiro[4.5]decane*

The compound was synthesised in an analogous way to Method 43a but using 1,4-dioxa-8-azaspiro[4.5]decane as starting material rather than pyrrolidin-3-ol (yield, 72%). ^1H NMR (400 MHz, $CDCl_3$): 1.6-1.8 (m, 4H), 2.3-2.3 (m, 4H), 2.9 (t, 2H), 3.0 (qn, 1H), 3.4 (t, 2H), 3.9 (s, 4H), 4.4 (s, 1H), 7.1-7.5 (m, 10H); MS: m/z 365 (M^+).

(b) *8-Azetidin-3-yl-1,4-dioxa-8-azaspiro[4.5]decane*

8-[1-(Diphenylmethyl)azetidin-3-yl]-1,4-dioxa-8-azaspiro[4.5]decane (0.5 g, 1.4 mmol) was dissolved in dry CH_2Cl_2 under nitrogen and to the resultant solution was added 1-chloroethyl chloroformate (0.45 mL, 4.1 mmol) at 0°C. The mixture was stirred for 1.5h and then methanol was added. The solution was heated to reflux for 20 min and then the solvent was removed by evaporation. The residue was triturated with acetone and the precipitate was then recrystallised from isopropyl alcohol. There was obtained 235 mg (73%) of 8-azetidin-3-yl-1,4-dioxa-8-azaspiro[4.5]decane hydrochloride as a solid. MS: m/z 199 (M^+).

Method 45

1-[(3*S*)-4-[(3-cyano-1-naphthoyl)(methyl)amino]-3-(3,4-dichlorophenyl)butyl]azetidin-3-yl methanesulfonate

(a) *3-Cyano-N-[(2S)-2-(3,4-dichlorophenyl)-4-(3-hydroxyazetidin-1-yl)butyl]-N-methyl-1-naphthamide*

3-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide (*WO 00/02859;* 1.0 g, 2.3 mmol) was dissolved in CH_2Cl_2 (10 mL) and to the resultant solution were added azetidin-3-ol hydrochloride (0.24 g, 2.2 mmol) and triethylamine (0.30 mL, 2.2 mmol). After stirring for 40 min, sodium triacetoxyborohydride (0.65 g, 3.1 mmol) was added and the solution was stirred at room temperature for 3 h. The solvent was removed by evaporation and the residue was partitioned between saturated aqueous $NaHCO_3$ solution and ethyl acetate. The solvent was removed by evaporation and the residue was dissolved in hydrochloric acid (1M). The solution was washed with CH_2Cl_2, alkalised with aqueous NaOH (2M) and then extracted with CH_2Cl_2. The solvent was removed by evaporation and there was obtained 0.85 g (80%) of 3-cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-hydroxyazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 0.8-4.4 (cm, 15H), 6.4-8.2 (cm, 8H), 8.6 (d, 1H); MS: m/z 482 (M^+).

(b) *1-[(3S)-4-[(3-cyano-1-naphthoyl)(methyl)amino]-3-(3,4-dichlorophenyl)butyl]azetidin-3-yl methanesulfonate*

3-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-hydroxyazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide (0.20 g, 0.41 mmol) was dissolved in CH_2Cl_2 and to the resultant solution was added triethylamine (0.17 mL, 0.41 mmol). The mixture was cooled to 0°C before careful addition of methanesulfonyl chloride (0.03 mL, 0.41 mmol). The mixture was stirred with cooling for 30 min and then at RT for 1 h. The reaction mixture was diluted with CH_2Cl_2 and then washed with hydrochloric acid (1M), saturated $NaHCO_3$ and then with brine. The organic solution was dried over $MgSO_4$ and the solvent removed by evaporation. There was obtained 0.21 g (92%) of 1-[(3*S*)-4-[(3-cyano-1-naphthoyl)(methyl)amino]-3-(3,4-dichlorophenyl)butyl]azetidin-3-yl methanesulfonate as a solid. MS: m/z 560 (M^+).

Method 46

3-Cyano-*N*-[2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide

(a) *2-(4-Fluorophenyl)-N-methylpent-4-enamide*

2-(4-Fluorophenyl)pent-4-enoic acid (*Bioorg. Med. Chem. Lett. 2000, 1893*; 4.20 g, 21.6 mmol) was dissolved in CH_2Cl_2 (75 mL) and to the resultant solution was added TBTU (7.29 g, 22.7 mmol). The mixture was stirred at RT for 15 min and then methylamine (11.9 mL of 2M THF solution, 23.8 mmol) and DIPEA (11.2 g, 86.5 mmol) were added. The reaction mixture was stirred at RT for 3 h, subsequently diluted with CH_2Cl_2 (50 mL) and then washed several times with water. The solvent was removed by evaporation and the residue flash chromatographed on silica gel (heptane-ethyl acetate, 1:1). There was obtained 3.5 g (78%) of 2-(4-fluorophenyl)-*N*-methylpent-4-enamide as an oil, which shortly after crystallized. ^{1}H NMR (400 MHz, $CDCl_3$): 2.5 (qn, 1H), 2.7 (d, 3H), 2.9 (qn, 1H), 3.4 (t, 1H), 4.9-5.1 (m, 2H), 5.6-5.8 (m, 1H), 6.0-6.2 (b, 1H), 7.0 (m, 2H), 7.3 (m, 2H).

(b) *[2-(4-Fluorophenyl)pent-4-en-1-yl]methylamine*

Lithium aluminium hydride (0.11 g, 2.9 mmol) was slurried in ether (15 mL) under nitrogen with stirring. A solution of 2-(4-fluorophenyl)-*N*-methylpent-4-enamide (0.20 g in 5 mL of ether, 0.97 mmol) was added carefully and the mixture was then stirred at RT overnight. Water (0.11 mL) was added dropwise followed by a solution of NaOH (0.11 mL of a 15% aqueous solution) and then water (0.33 mL) again. The mixture was stirred for 10 min and then filtered. The filter cake was washed with ether and the combined solutions were washed several times with water. The organic solution was dried over $MgSO_4$ and the solvent was removed by evaporation. There was obtained 0.16 g (86%) of [2-(4-fluorophenyl)pent-4-en-1-yl]methylamine as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): 2.4-2.6 (m, 5H), 2.7-2.9 (m, 3H), 4.9-5.0 (m, 2H), 5.6-5.8 (m, 1H), 7.0 (m, 2H), 7.1 (m, 2H); MS: m/z 194 (M^+).

(c) *3-Cyano-N-[2-(4-fluorophenyl)pent-4-en-1-yl]-N-methyl-1-naphthamide*

[2-(4-Fluorophenyl)pent-4-en-1-yl]methylamine (1.0 g, 5.2 mmol) was dissolved in CH_2Cl_2 and stirred at 0°C during addition of DIPEA (1.5 g, 11.4 mmol) and 3-cyano-1-naphthoyl chloride (Method 51; 1.1 g, 5.17 mmol). The mixture was stirred with cooling for a short while and then stirred at RT for 2 h. The mixture was washed twice with water,

once with an aqueous solution of $KHSO_4$, and then with brine. The solvent was removed by evaporation and the residue flash chromatographed on silica gel (methanol- CH_2Cl_2, 5:95). There was obtained 1.55 g (80%) of 3-cyano-*N*-[2-(4-fluorophenyl)pent-4-en-1-yl]-*N*-methyl-1-naphthamide as an oil. ^1H NMR (400 MHz, $CDCl_3$): 2.1-4.9 (cm, 8H), 5.0-5.1 (m, 2H), 5.6-5.8 (m, 1H), 6.4-8.0 (cm, 9H), 8.2 (s, 1H).

(d) *3-Cyano-N-[2-(4-fluorophenyl)-4-oxobutyl]-N-methyl-1-naphthamide*

3-Cyano-*N*-[2-(4-fluorophenyl)pent-4-en-1-yl]-*N*-methyl-1-naphthamide (1.5 g, 4.03 mmol) was dissolved in a mixture of acetone (30 mL), *tert*-butanol (15 mL) and water (7.5 mL) and stirred at RT during addition of OsO_4 (0.40 mL of 2.5% in *tert*-butanol, 0.04 mmol). 4-Methylmorpholine *N*-oxide (2.08 g, 17.8 mmol) was added and the mixture was stirred at RT overnight. A saturated aqueous solution of sodium bisulfite (15 mL) was added and the mixture stirred for 5 min and then concentrated. The residue was diluted with water (100 mL) and then extracted trice with CH_2Cl_2. The combined organic solutions were washed with brine and the solvent removed by evaporation. The residue was dissolved in a mixture of THF (21 mL) and water (7 mL) whereupon sodium periodate (0.95 g, 4.43 mmol) was added. The solution was stirred at RT overnight and then diluted with water (150 mL) and brine (75 mL). The mixture was extracted trice with ethyl acetate and the combined organic solutions were washed with water and then with brine. The solvent was removed by evaporation and the residue flash chromatographed on silica gel (ethyl acetate- heptane, 7:3). There was obtained 1.43 g (95%) of 3-cyano-*N*-[2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): 2.4-4.4 (cm, 8H), 6.8-8.0 (cm, 9H), 8.2 (s, 1H), 9.8 (s, 1H).

Method 47

3-Cyano-*N*-[2-(4-cyanophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide

(a) *[2-(4-Bromophenyl)-4-[(triisopropylsilyl)oxy]butyl]methylamine*

3-(4-Bromophenyl)-4-(methylamino)butan-1-ol (*Chem. Pharm. Bull. 46, 1998, 242*; 1.77 g, 6.86 mmol) was dissolved in CH_2Cl_2 (100 mL) at 0°C under argon. Imidazole (1.22 g, 17.9 mmol) was added, the mixture stirred for 10 min and then triisopropylchlorosilan (3.16g, 16.4 mmol) was added with cooling. The mixture was stirred at RT temperature for 48 h and then washed twice with water (100 mL) and brine. The solvent was removed by

evaporation and the residue flash chromatographed on silica gel (CH_2Cl_2 – Methanol - NH_4OH, 15:1:0.1). There was obtained 2.17 g (75%) of {2-(4-Bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylamine as an oil. ^1H NMR (300 MHz, $CDCl_3$): 0.9-1.1 (m, 21H), 1.6-1.9 (m, 2H), 2.4 (s, 3H), 2.7-2.8 (m, 2H), 3.0-3.1 (m, 1H), 3.4-3.6 (m, 2H), 7.1 (d, 2H), 7.4 (d, 2H).

(b) *tert-Butyl {2-(4-bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate*

{2-(4-Bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylamine (0.95 g, 2.3 mmol) and 4-dimethylaminopyridine (0.34 g, 2.8 mmol) were dissolved in dry CH_2Cl_2 (10 mL) under nitrogen. Boc-anhydride (1.1 g, 5.1 mmol) was added at 0°C and the mixture was stirred at RT for 48 h and then washed twice with brine. The solution was dried over Na_2SO_4 and the solvent was removed by evaporation. The residue was flash chromatographed on silica gel (hexane-ether, 40:1 to 8:1). There was obtained 1.66 g (73%) of *tert*-Butyl {2-(4-bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate as an oil. ^1H NMR (300 MHz, $CDCl_3$): 0.9-1.1 (m, 21H), 1.4 (s, 9H), 1.7-1.9 (m, 2H), 2.7 (m, 3H), 3.2-3.6 (m, 5H), 7.0-7.1 (m, 2H), 7.3-7.4 (m, 2H).

(c) *tert-Butyl {2-(4-cyanophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate*

tert-Butyl {2-(4-bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate (1.16 g, 2.25 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.62 g, 0.68 mmol) and tri-*o*-tolylphosphine (1.03 g, 3.38 mmol) were mixed together with acetonitrile (3 mL) and DMF (3 mL) under argon. Zinc cyanide (0.16 g, 1.35 mmol) was added and the mixture was stirred at 81°C for 24h and then concentrated. Ethyl acetate was added to the residue and the slurry was filtered through a micro filter. The solvent was removed by evaporation and the residue purified by flash chromatography (hexane-ether, 10:1). There was obtained 0.43 g, (41%) of *tert*-butyl {2-(4-cyanophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate as a solid. ^1H NMR (300 MHz, $CDCl_3$): 0.9-1.1 (m, 21H), 1.4 (s, 9H), 1.7-1.9 (m, 2H), 2.7 (m, 3H), 3.2-3.6 (m, 5H), 7.3-7.4 (m, 2H), 7.5-7.6 (m, 2H); MS: m/z 361 (M^+).

(d) *4-{3-Hydroxy-1-[(methylamino)methyl]propyl}benzonitrile*

tert-Butyl {2-(4-cyanophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate (0.37 g) was dissolved in THF (8 mL) at 0°C. Hydrochloric acid (8 ml of 6M solution) was added and the mixture stirred overnight at RT. The volatiles were removed by evaporation and then removed azeotropically after the addition of methanol (5x50 mL). The residue was dissolved in water and the solution alkalised to pH 8-9 by the addition of Na_2CO_3 (s) and then extracted trice with ethyl acetate (100 mL). The organic solution was dried over Na_2SO_4 and then evaporated. The product was purified by flash chromatography (CH_2Cl_2-MeOH-NH_4OH, 9:1:0.1). There was obtained 0.10 g, 60%) of 4-{3-Hydroxy-1-[(methylamino)methyl]propyl}benzonitrile as a solid. ^1H NMR (300 MHz, $CDCl_3$): 1.9-2.0 (m, 2H), 2.5 (s, 3H), 2.8-2.9 (m, 3H), 3.4-3.7 (m, 3H), 3.7 (m, 1H), 7.3 (d, 2H), 7.6 (d, 2H); MS: m/z 205 (M^+).

(e) *3-Cyano-N-[2-(4-cyanophenyl)-4-hydroxybutyl]-N-methyl-1-naphthamide*

4-{3-Hydroxy-1-[(methylamino)methyl]propyl}benzonitrile (0.55 g, 2.69 mmol) and DIPEA (0.77 g, 5.9 mmol) were dissolved in CH_2Cl_2 (5 mL). 3-Cyano-1-naphthoyl chloride (Method 51; 0.58 g, 2.69 mmol) was added in portions with stirring and cooling (external ice-bath). The mixture was stirred for 2 h with cooling and then diluted with CH_2Cl_2 (10 mL). The solution was washed twice with water, twice with a saturated aqueous $KHSO_4$ solution and then with brine. The solvent was removed by evaporation and the residue flash chromatographed on silica gel (CH_2Cl_2-MeOH, 9:1). There was obtained 0.70 g (67%) of 3-cyano-N-[2-(4-cyanophenyl)-4-hydroxybutyl]-*N*-methyl-1-naphthamide as a white solid. ^1H NMR (400 MHz, $CDCl_3$): 1.4-2.5 (cm, 2H), 2.6 (s, 3H), 3.1-4.6 (cm, 6H), 6.4-7.8 (cm, 8H), 7.9 (d, 1H), 8.2 (s, 1H); MS: m/z 384 (M^+).

(f) *3-Cyano-N-[2-(4-cyanophenyl)-4-oxobutyl]-N-methyl-1-naphthamide*

3-Cyano-*N*-[2-(4-cyanophenyl)-4-hydroxybutyl]-*N*-methyl-1-naphthamide (0.70 g, 1.8 mmol) was dissolved in CH_2Cl_2 (15 mL) and to the resultant solution was added Dess Martin Periodinane (0.85 g, 2.0 mmol) in portions. The mixture was stirred at RT overnight and then sodium thiosulfate (1.9 g, 12 mmol), dissolved in saturated $NaHCO_3$ solution (30 mL), was added. The mixture was stirred vigorously for 2h and then the organic solution was washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation and the residue purified by flash chromatography (ethyl acetate-heptane,

4:1). There was obtained 0.50 g, (43%) of 3-cyano-*N*-[2-(4-cyanophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 2.7 (s, 3H), 2.9-4.4 (cm, 5H), 6.4-7.8 (cm, 8H), 7.9 (d, 1H), 8.2 (s, 1H), 9.8 (s, 1H); MS: m/z 382 (M^+).

Method 48

Thiomorpholine 1,1-dioxide dihydrochloride

(a) *4-[1-(Diphenylmethyl)azetidin-3-yl]thiomorpholine 1,1-dioxide*

The compound was synthesised in an analogous way to Method 43a but using thiomorpholine 1,1-dioxide (*J. Chem. Soc. 1949, 3433*) rather than pyrrolidin-3-ol (yield, 19%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.7-2.8 (m, 4H), 2.8-2.9 (m, 2H), 3.0-3.1 (m, 4H), 3.2 (qn, 1H), 3.4 (m, 2H), 4.4 (s, 1H), 7.1-7.4 (m, 10H); MS: m/z 357 (M^+).

(b) *Thiomorpholine 1,1-dioxide dihydrochloride*

The compound was synthesised in an analogous way to Method 43b but using 4-[1-(diphenylmethyl)azetidin-3-yl]thiomorpholine 1,1-dioxide rather than 1-[1-(diphenylmethyl)azetidin-3-yl]pyrrolidin-3-ol (yield, 89%). ^{1}H NMR (400 MHz, D_2O): 3.2-3.4 (b, 4H), 3.4-3.5 (m, 4H), 4.2 (m, 1H), 4.2-4.4 (4H).

Method 49

1-Azetidin-3-ylpiperidin-4-ol dihydrochloride

(a) *1-[1-(Diphenylmethyl)azetidin-3-yl]piperidin-4-ol*

The compound was synthesised in an analogous way to Method 43a but using piperidin-4-ol rather than pyrrolidin-3-ol (yield, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.5-1.6 (m, 2H), 1.8 (m, 2H), 2.0 (m, 2H), 2.6 (m, 2H), 2.8-3.0 (m, 3H), 3.4 (m, 2H), 3.6-3.7 (m, 1H), 4.4 (s, 1H), 7.1-7.5 (m, 10H); MS: m/z 323 (M^+).

(b) *1-Azetidin-3-ylpiperidin-4-ol dihydrochloride*

The compound was synthesised in an analogous way to Method 43b but using 1-[1-(diphenylmethyl)azetidin-3-yl]piperidin-4-ol rather than 1-[1-(diphenylmethyl)azetidin-3-yl]pyrrolidin-3-ol (yield, 89%). ^{1}H NMR (400 MHz, DMSO-d_6): 1.6-5.0 (cm, 13H), 9.0-9.4 (b, 1H), 9.8-10.2 (b, 1H), 12.0-12.8 (b, 1H).

Method 50

2-(4-Fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine hydrochloride

(a) *tert-Butyl [2-(4-fluorophenyl)pent-4-en-1-yl]methylcarbamate*

[2-(4-fluorophenyl)pent-4-en-1-yl]methylamine (Method 46b; 11.2 g, 190 mmol) was dissolved in THF (350 mL) and to the solution was added triethylamine (8.7 ml, 100 mmol). The mixture was cooled on an ice-bath and di-*tert*-butyldicarbonate (15 g, 218 mmol) was added. The ice-bath was removed and the reaction mixture was allowed to reach room temperature and then stirred overnight. Ether was added and the mixture was washed with water. The organic layer was dried ($MgSO_4$) and the solvent removed by evaporation. There was obtained 16.5g (29%) of *tert*-butyl [2-(4-fluorophenyl)pent-4-en-1-yl]methylcarbamate as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 1.4 (s, 9H), 2.2-2.4 (m, 2H), 2.5-2.7 (cm, 3H), 2.8-3.8 (cm, 3H), 4.8-5.0 (cm, 2H), 5.5-5.7 (m, 1H), 6.9 (t, 2H), 7.1 (b, 2H).

(b) *1-[(tert-butoxycarbonyl)(methyl)amino]-1,2,3-trideoxy-2-(4-fluorophenyl)pentitol*

tert-Butyl [2-(4-fluorophenyl)pent-4-en-1-yl]methylcarbamate (17.0 g, 57.9 mmol) was dissolved in a mixture of acetone, *t*-butanol and water (190 mL, 2:1:1). OsO_4 (3ml, 2.5% t-butanol solution) was added at rt and after stirring for 10 minutes, NMO (27.1 g, 231 mmol) was added. The mixture was stirred overnight and then the reaction mixture was quenched by adding an aqueous solution of 20% sodium bisulfite. The mixture was stirred for 15min and then diluted with water. The solution was extracted with CH_2Cl_2 and the organic extract was washed with brine, dried and concentrated on a rotavapor. There was obtained 19.4 g (100%) of crude 1-[(*tert*-butoxycarbonyl)(methyl)amino]-1,2,3-trideoxy-2-(4-fluorophenyl)pentitol as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.3 (s, 9H), 1.4-1.8 (cm, 2H), 2.0-3.6 (cm, 11H), 6.9 (t, 2H), 7.1 (b, 2H).

(c) *tert-Butyl [2-(4-fluorophenyl)-4-oxobutyl]methylcarbamate*

1-[(*tert*-butoxycarbonyl)(methyl)amino]-1,2,3-trideoxy-2-(4-fluorophenyl)pentitol (19.4 g, 59.2 mmo) was dissolved in a mixture of THF and water (3:1) and to the solution was added $NaIO_4$ (17.7 g, 82.9 mmol). After stirring for 6 h the reaction mixture was diluted with water and the mixture was extracted with ethyl acetate. The organic extract

was washed with brine, dried and concentrated on a rotavapor. There was obtained *tert*-Butyl [2-(4-fluorophenyl)-4-oxobutyl]methylcarbamate as a yellow oil. ^{13}C NMR (100 MHz, $CDCl_3$): 28.4 (s), 35.1 (d), 38 (m), 47.3 (d), 54.6 (d), 79.8 (s), 115.7 (d), 129.4 (d), 137.2 (s), 155.8 (m), 160.7 (s), 163.2 (s), 200.6 (d).

(d) *tert-Butyl [2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate*

tert-Butyl [2-(4-fluorophenyl)-4-oxobutyl]methylcarbamate (0.50 g, 1.7 mmol) and 4-azetidin-3-ylthiomorpholine dihydrochloride (0.45 g, 2.0 mmol) were dissolved in methanol (30 mL). A methanolic solution (15 mL) of sodium cyano borohydride (0.71 g, 11.2 mmol) and zinc chloride (0.77 g, 5.6 mmol) was added and the mixture stirred for 1 h at RT. The solvent was removed by evaporation and the residue was partitioned between a saturated solution of $NaHCO_3$ aq and ethyl acetate. The organic solution was evaporated and the product was purified by reversed phase chromatography using a mixture of acetonitrile and 0.1 M ammonium acetate aq. There was obtained 350 mg (41%) of *tert*-butyl [2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): 1.3 (s, 9H), 1.6-1.7 (m, 2H), 2.0 (s, 1H), 2.3-2.7 (m, 13H), 2.8-3.6 (m, 6H), 3.6-3.7 (m, 2H), 6.9-7.1 (m, 4H), 10.2-10.4 (b,1H); MS: m/z 438 (M^+).

(e) *2-(4-Fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine hydrochloride*

tert-Butyl [2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate (0.27 g, 0.62 mmol) was dissolved in a mixture of HCl and dioxane (4M HCl in dioxane). The solution was stirred overnight at RT and then the volatiles were removed by evaporation. There was obtained 0.26 mg (100%) of 2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine hydrochloride as a solid. ^1H NMR (400 MHz, CD_3OD): 1.8-2.1 (2H), 2.7 (s, 3H), 2.9-4.6 (m, 18H), 7.2 (t, 2H), 7.4 (m, 2H); MS: m/z 338 (M^+).

Method 51

3-Cyano-1-naphthoyl chloride

3-Cyano-1-naphthoic acid (*Bioorg. Med. Chem. Lett. 2001, 2769*; 1.1 g, 5.6 mmol) was slurried in CH_2Cl_2 (10 mL) and then oxalyl chloride was added with stirring. A drop of DMF was added and the mixture stirred at RT overnight under nitrogen. The solvent was removed by evaporation and there was obtained 1.2 g (100%) of 3-cyano-1-naphthoyl chloride as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): 7.7-7.8 (m, 1H), 7.8-7.9 (m, 1H), 8.0-8.1 (m, 1H), 8.5 (s, 1H), 8.7 (s, 1H), 8.8 (d, 1H).

Method 52

7-Chloro-2,3-dihydro-1,4-benzodioxine-5-carboxylic acid

(a) *5-Chloro-2,3-dihydroxybenzaldehyde*

5-Chloro-2-hydroxy-3-methoxy-benzaldehyde (*J. Org. Chem. 56; 1991; 5451;* 20.0 g, 107 mmol) was suspended in hydrobromic acid (100 mL of 47 % in water). The mixture was refluxed for 6 h and then cooled to RT before dilution with water (300 mL). The formed precipitate was collected by filtration and then washed with water. After air drying, the solid material was purified by soaking with CH_2Cl_2 (4 x 150 mL). There was obtained 6.0 g (32 %) of 5-chloro-2,3-dihydroxybenzaldehyde as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): 7.1 (d, 1H), 7.2 (d, 1H), 9.8 (s, 1H), 11.0 (s, 1H).

(b) *7-Chloro-2,3-dihydro-1,4-benzodioxine-5-carbaldehyde*

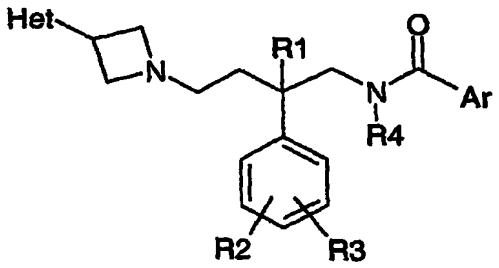
5-Chloro-2,3-dihydroxybenzaldehyde (6.0 g, 34.7 mmol) was dissolved in DMF (100 mL) and to the solution were added 1,2-dibromoethane (8.0 g, 42.5 mmol) and potassium carbonate (10.0 g, 70 mmol). The mixture was stirred at 100°C for one hour, cooled to RT and then diluted with water (200 mL). After extraction twice with ethyl acetate (200 mL) the combined organic solutions were washed with brine and then dried over Na_2SO_4. The solvent was removed by evaporation and the solid residue treated with methanol. After filtration and drying there was obtained 6.5 g (94 %) of 7-chloro-2,3-dihydro-1,4-benzodioxine-5-carbaldehyde. ^{1}H NMR (300 MHz, $CDCl_3$): 4.3-4.4 (m, 4H), 7.1 (d, 1H), 7.3 (d, 1H), 10.3 (s, 1H).

(c) *7-chloro-2,3-dihydro-1,4-benzodioxine-5-carboxylic acid*

7-Chloro-2,3-dihydro-1,4-benzodioxine-5-carbaldehyde (6.25 g, 31.4 mmol) was dissolved in acetone and the solution was then cooled to 5°C. A solution of CrO_3 in sulfuric acid (4 M in 4 M H_2SO_4, 12.5 mL, 50 mL) was added dropvise over 2 min and the mixture was refluxed for 30 min. Water (150 mL) was added and then most of the acetone was removed by evaporation. The mixture was extracted with ether (150 mL) and the organic solution was then extracted with a solution of NaOH (0.5 M, 150 mL). The aqueous solution was acidified with 2 M hydrochloric acid and then extracted with ether (150 mL). The organic solution was washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation and the residue treated with CH_2Cl_2. After filtration and drying there was obtained 5.2 g (77 %) of 7-chloro-2,3-dihydro-1,4-benzodioxine-5-carboxylic acid. ^1H NMR (400 MHz, acetone-d_6): 4.3-4.4 (m, 4H), 7.1 (d, 1H), 7.3 (d, 1H), 11-12 (b, 1H).

Claims

1. A compound having the general formula (I)



wherein

Het is a heterocyclic ring containing one or more nitrogen atoms

R1 is hydrogen, hydroxy or lower alkyl

R2 and R3 are independently hydrogen, lower alkoxy, halo, CF_3 or cyano, provided that both are not hydrogen

R4 is lower alkyl

Ar is an optionally substituted aromatic ring system selected from phenyl, pyridinyl, 1-naphthyl, 5,6,7,8-tetrahydro-1-naphthyl, quinolinyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinazolin-4-yl, 1-benzo[b]thiophen-7-yl, 1-benzo[b]thiophen-4-yl, 1-benzo[b]thiophen-3-yl, isoquinolinyl, quinazolinyl and indan-4-yl,

as a free base or any salt thereof

with the proviso that compounds of formula (I) wherein Ar is unsubstituted phenyl are excluded.

2. A compound according to claim 1, characterized in that the heterocyclic ring Het is connected to the rest of the molecule at one of the nitrogen atoms of the ring.

3. A compound according to any one of claims 1 or 2, characterized in that the heterocyclic ring Het is selected from the group optionally substituted piperidino, optionally substituted azepano, optionally substituted pyrrolidino, optionally substituted morpholino, optionally substituted oxazepano, optionally substituted thiomorpholino, optionally substituted thiazepano and optionally substituted piperazino.

4. A compound according to claim 3, characterized in that the heterocyclic ring Het is piperidino optionally substituted at its four position with hydroxy, oxo, methylthio, methylsulfinyl, methylsulfonyl, cyano, 1,3-dioxolan-2-yl, lower alkoxy, amino optionally mono or disubstituted with lower alkyl, acylamino optionally N-substituted with lower alkyl, (lower alkylsulfonyl)amino optionally N-substituted with lower alkyl, or one or two fluoro atoms.

5. A compound according to claim 3, characterized in that the heterocyclic ring Het is pyrrolidino optionally being substituted at its three position with fluoro, hydroxy or oxo.

6. A compound according to claim 3, characterized in that the heterocyclic ring Het is morpholino or thiomorpholino optionally being substituted at its sulfur with one or two oxygen.

7. A compound according to claim 3, characterized in that the heterocyclic ring Het is piperazino optionally being substituted at the 4-nitrogen atom with lower alkyl, lower alkyl sulfonyl, lower acyl or lower alkyl together with oxygen.

8. A compound according to claim 1, characterized in that R1 is hydrogen.

9. A compound according to claim 1, characterized in that R2 and R3 are both chloro or one is fluoro and the other is hydrogen.

10. A compound according to claim 9, characterized in that R2 and R3 are both chloro and attached in the three and four position of the phenyl ring or R2 is fluoro attached in the four position and R3 is hydrogen.

11. A compound according to claim 1, characterized in that R4 is methyl.

12. A compound according to claim 1, characterized in that Ar may optionally be substituted at one or more of its carbon atoms in its aromatic moiety with one or more groups independently selected from cyano, halo, lower alkyl, lower alkoxy, nitro, trifluoromethoxy, difluoromethoxy, trifluoromethyl, lower alkylsulfinyl, lower alkylsulfonyl, lower alkylthio and trifluoromethylsulfonyloxy.

13. A compound according to claim 1, characterized in that
Het is thiomorpholino, morpholino or oxidothiomorpholino,
R1 is H,
R2 and R3 are fluoro and hydrogen, respectively, fluoro being preferably in para position,
Ar is 3-cyano-5,6,7,8-tetrahydro-1-naphthyl.

14. A compound according to claim 1 selected from
N-[(2S)-2-(3,4-dichlorophenyl)-4-(3-oxidothiomorpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-3,5-bis(trifluoromethyl)benzamide acetate,

3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide acetate,
3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide acetate,

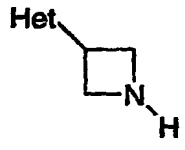
3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(4-hydroxypiperidin-1-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide,

3-cyano-*N*-[2-(4-fluorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide,

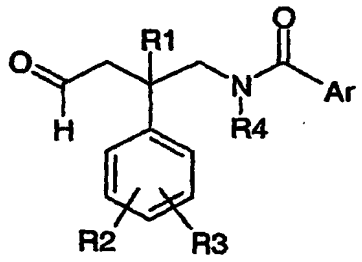
3-cyano-*N*-{2-(4-fluorophenyl)-4-[3-(4-hydroxypiperidin-1-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide, and

4-fluoro-*N*-[2-(4-fluorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide.

15. A process for preparing a compound according to any one of claims 1-14, which process comprises a) reacting a compound of the formula (III) with a compound of the formula (IV):



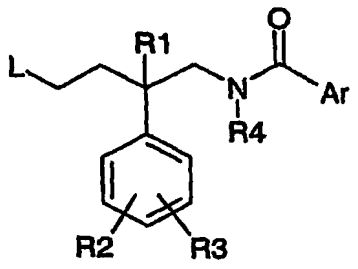
(III)



(IV)

wherein R1-R4, Het, and Ar are as hereinbefore defined; and the conditions are such that reductive alkylation of the compounds of the formulae (III) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formulae (III) and the carbon atom of the aldehyde group of the compounds of formulae (IV); or

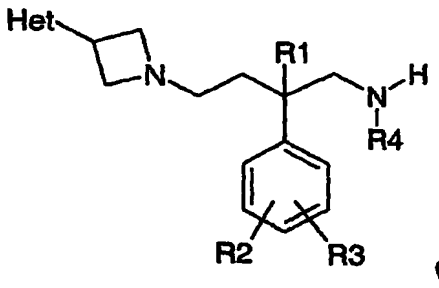
b) reacting a compound of the formula (III) with a compound of the formula (V):



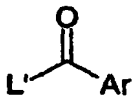
(V)

wherein R1-R4, Het, and Ar are as hereinbefore defined; and L is a group such that alkylation of the compounds of the formulae (III) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formulae (III) and the carbon atom of the compounds of formulae (V) that is adjacent to the L group; or

c) reacting a compound of the formula (VI) with a compound of the formula (VII):



(VI)



(VII)

wherein R1-R4, Het and Ar are as hereinbefore defined; and L' is a leaving group; wherein any other functional group is protected, if necessary, and:

i) removing any protecting groups;

ii) optionally oxidizing any oxidizeable atoms;

iii) optionally forming a pharmaceutically acceptable salt.

16. *tert*-Butyl [(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate,

[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine,

[(2*S*)-2-(3,4-dichlorophenyl)-4-[3-(1-oxidothiomorpholin-4-yl)azetidin-1-yl]butyl]methylamine,

1-[1-(diphenylmethyl)azetidin-3-yl]pyrrolidin-3-ol,

8-[1-(diphenylmethyl)azetidin-3-yl]-1,4-dioxa-8-azaspiro[4.5]decane,

8-azetidin-3-yl-1,4-dioxa-8-azaspiro[4.5]decane,

3-cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-hydroxyazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide,

3-cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-(3-hydroxyazetidin-1-yl)butyl]-*N*-methyl-1-naphthamide,

tert-butyl [2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylcarbamate,

[2-(4-fluorophenyl)-4-(3-thiomorpholin-4-ylazetidin-1-yl)butyl]methylamine,

ethyl 5-cyano-1-benzothiophene-7-carboxylate,

5-cyano-1-benzothiophene-7-carboxylic acid,

3-cyano-*N*-[2-(4-fluorophenyl)pent-4-en-1-yl]-*N*-methyl-1-naphthamide,

3-cyano-*N*-[2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide,

{2-(4-bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylamine,

tert-butyl {2-(4-bromophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate,

tert-butyl {2-(4-cyanophenyl)-4-[(triisopropylsilyl)oxy]butyl}methylcarbamate,

4-{3-hydroxy-1-[(methylamino)methyl]propyl}benzonitrile,

3-cyano-*N*-[2-(4-cyanophenyl)-4-hydroxybutyl]-*N*-methyl-1-naphthamide,

3-cyano-*N*-[2-(4-cyanophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide,

tert-butyl [2-(4-fluorophenyl)pent-4-en-1-yl]methylcarbamate,

1-[(*tert*-butoxycarbonyl)(methyl)amino]-1,2,3-trideoxy-2-(4-fluorophenyl)pentitol,

tert-butyl [2-(4-fluorophenyl)-4-oxobutyl]methylcarbamate, or

7-chloro-2,3-dihydro-1,4-benzodioxine-5-carbaldehyde

as a free base or any salt thereof.

17. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1-14 as a single enantiomer, a racemate or a mixture thereof in the form of a free base or a pharmaceutically acceptable salt or solvate thereof optionally in association with diluents, excipients or inert carriers.

18. Use of the compound according to any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the prevention or treatment of respiratory, cardiovascular, neuro, pain, oncology, inflammatory and/or gastrointestinal disorders.

19. The use of the compound according to claim 18, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the prevention or treatment of asthma, allergic rhinitis, pulmonary, cough, cold, inflammation, chronic obstructive pulmonary disease, airway reactivity, urticaria, hypertension, rheumatoid arthritis, edema, angiogenesis, pain, migraine, tension headache, psychoses, depression, anxiety, Alzheimer's disease, schizophrenia, Huntington's disease, bladder hypermotility, urinary incontinence, eating disorder, manic depression, substance dependence, movement disorder, cognitive disorder, obesity, stress disorders, micturition disorders, mania, hypomania and aggression, bipolar disorder, cancer, carcinoma, gastrointestinal hypermotility, gastric asthma, Crohn's disease, gastric emptying disorders, ulcerative colitis, irritable bowel syndrome, inflammatory bowel disease, emesis, gastric motility disorders or gastro-esophageal reflux disease (GERD).

20. A method of preventing or treating respiratory, cardiovascular, neuro, pain, oncology and/or gastrointestinal disorders comprising administering an effective amount of the compound according to any one of claims 1-14.

21. The method according to claim 20 wherein gastrointestinal hypermotility, gastric asthma, Crohn's disease, gastric emptying disorders, ulcerative colitis, irritable bowel syndrome, inflammatory bowel disease, emesis, gastric motility disorders or gastro-esophageal reflux disease (GERD) is prevented or treated.

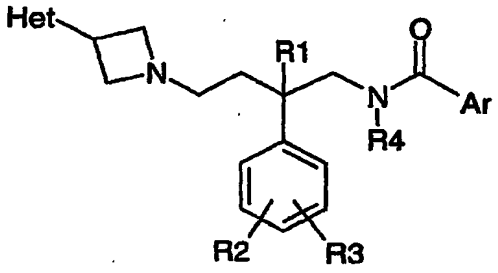
22. A compound as defined in any of claims 1-14 for use in therapy.

23. A compound as defined in claim 22 for use in the prevention or treatment of respiratory, cardiovascular, neuro, pain, oncology, inflammatory and/or gastrointestinal disorders.

24. A compound as defined in claim 23 for use in the prevention or treatment of asthma, allergic rhinitis, pulmonary, cough, cold, inflammation, chronic obstructive pulmonary disease, airway reactivity, urticaria, hypertension, rheumatoid arthritis, oedema, angiogenesis, pain, migraine, tension headache, psychoses, depression, anxiety, Alzheimer's disease, schizophrenia, Huntington's disease, bladder hypermotility, urinary incontinence, eating disorder, manic depression, substance dependence, movement disorder, cognitive disorder, obesity, stress disorders, micturition disorders, mania, hypomania and aggression, bipolar disorder, cancer, carcinoma, fibromyalgia, non cardiac chest pain, gastrointestinal hypermotility, gastric asthma, Crohn's disease, gastric emptying disorders, ulcerative colitis, irritable bowel syndrome, inflammatory bowel disease, emesis, gastric motility disorders or gastro-esophageal reflux disease (GERD).

25. A compound as defined in any of claims 1-14 for use as an NK_1/NK_2 antagonist.

26. A compound having the general formula (I)



wherein

Het is a heterocyclic ring containing one or more nitrogen atoms

R1 is hydrogen, hydroxy or lower alkyl

R2 and R3 are independently hydrogen, lower alkoxy, halo, CF_3 or cyano, provided that both are not hydrogen

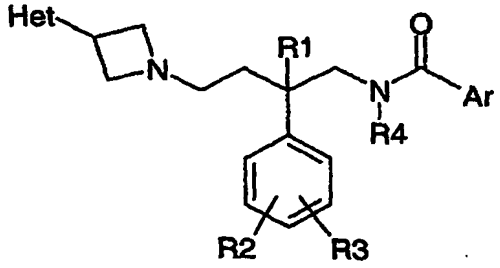
R4 is lower alkyl

Ar is an optionally substituted aromatic ring system selected from substituted phenyl, pyridinyl, 1-naphthyl, 5,6,7,8-tetrahydro-1-naphthyl, quinolinyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinazolin-4-yl, 1-benzo[b]thiophen-7-yl, 1-benzo[b]thiophen-4-yl, 1-benzo[b]thiophen-3-yl, isoquinolinyl, quinazolinyl and indan-4-yl,

as a free base or any salt thereof.

ABSTRACT

The present invention relates to a compound having the general formula (I)



wherein

Het is a heterocyclic ring containing one or more nitrogen atoms

R1 is hydrogen, hydroxy or lower alkyl

R2 and R3 are independently hydrogen, lower alkoxy, halo, CF_3 or cyano, provided that both are not hydrogen

R4 is lower alkyl

Ar is an optionally substituted aromatic ring system selected from phenyl, pyridinyl, 1-naphthyl, 5,6,7,8-tetrahydro-1-naphthyl, quinolinyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinazolin-4-yl, 1-benzo[b]thiophen-7-yl, 1-benzo[b]thiophen-4-yl, 1-benzo[b]thiophen-3-yl, isoquinolinyl, quinazolinyl and indan-4-yl,

with the proviso that compounds of formula (I) wherein Ar is unsubstituted phenyl are excluded, as a free base or any salt thereof, to pharmaceutical composition containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of compounds of formula I and to new intermediates used in the preparation thereof.